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THE NATH LAW GROUP 112 South West Street Alexandria, VA 22314			SAUCIER, SANDRA E	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,988	MEIR, URL	
	Examiner Sandra Saucier	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 06 November 2008.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 78,98-115 and 119-123 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 78,98-115, 119-123 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ . | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

Claims 78, 98–115, 119–123 are pending and are under examination.

Claim Rejections – 35 USC § 112

Claims 78, 98–115, 119–123 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the freezing of semen from different species with a cryoprotectant, does not reasonably provide enablement for the freezing any biological matter, particularly with no cryoprotectant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The invention is in the field of cryopreservation of biological matter for future medical/veterinary use.

The working examples are all directed to the freezing/thawing of suspension of sperm in extenders which contain cryoprotectants such as glycerol, glucose, egg yolk etc..

The claims encompass the freezing of any biological matter including tissues, organs, and any type of cells with and without cryopreservatives.

The state of the art is as follows.

Freezing technology with regard to biological materials is an art with centuries of experimentation. The state of the art with regard to organs and tissues and “simple” multicellular structures is still far from satisfactory. Please see the review by Gosden [U] which teach that ovarian tissue banking which includes freezing of the tissue is still an experimental procedure (abstract). This means that it is not routine to freeze all types of tissue. See also the review by I.A.M. de Graaf *et al.* [V] where it is taught that tissue preservation by freezing is still not routine and that cryopreservation by vitrification appears to be the most promising route of cryopreservation for tissue and organs with

retention of viability/function of the tissue or organ. Further, organs, because of their size, are particularly susceptible to freezing injury.

A second consideration is the fact that even with single cell suspensions, not all cells react the same with regard to freezing protocol, in fact even with a single mammalian cell, the oocyte, there are significant species differences. See Dinnyes *et al.* [W], a review that states on page 722, "Although sperm cells have been frozen successfully in dogs and cats, cryopreservation of oocytes in dogs remains elusive."

Luvoni [X] on page 510 section 3.4, states that sperm cells and embryos of cats have been successfully frozen, but "freezing of [cat] oocytes is still considered experimental because adequate rates of survival, fertilization and embryo development of frozen oocytes have been reached mainly with murine oocytes.". Thus, even freezing of single cells with retention of function is dependant on cell type and even the species from which it is derived.

While the instant claims do not require any cryopreservative, the art of freezing cells or tissues without cryopreservatives is non-existent except in the food art. However, freezing food is distinct from the instant application where the frozen material is to be employed in medical procedures such as IVF, transplantation and other medically related purposes. The criteria for a successful freezing/thawing protocol of a frozen dinner is much lower than for a gamete, for example.

Also, the type of cryopreservative for a particular cell type is also critical and is an area of unpredictability. The type and concentration of cryopreservative is derived empirically, see Guillouzo *et al.* [U2] where for one cell type, hepatocytes, critical parameters are the choice of the cryoprotectant and the composition of the freezing medium (abstract). On page 9, it is disclosed that even the species from which the hepatocytes are derived requires changes in the freezing medium composition for best results.

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In short, freezing of cells, tissues and organs is still an art with great unpredictability in terms of successful freezing of even the various types of single cells in suspension, coupled with the unpredictability of the concentrations and types of cryoprotectants for each cell type.

Undue experimentation would be required to practice the invention as claimed due to the amount of experimentation necessary because of the limited amount of guidance and limited number of working examples in the specification, the nature of the invention, the state of the prior art, breadth of the claims and the unpredictability of the art.

DECLARATION OF P. PATRIZIO

The declaration of P. Patrizio under 37 CFR 1.132 filed 11/6/08 is insufficient to overcome the rejection of claims 78, 98-115, 119-123 based upon 35 USC §112, first paragraph as set forth in the last Office action because: no objective evidence has been presented. P. Patrizio's opinion is that the specification provides sufficient description for a skilled artisan to make and use a method of freezing at least semen without the necessity of including a cryoprotectant, and that one of ordinary skill in the art knows that freezing of semen from different species is possible without the inclusion of a cryoprotectant.

It is recognized that one can freeze anything without a cryoprotectant such as muscle tissue (steak) or pancreas (sweetbreads) or even brain and the thawed product would be suitable for food. However, the question is whether the thawed muscle tissue or pancreas or brain, frozen under such conditions is useful in the medical field for grafting as taught in the specification on page 1.

The declaration is directed primarily to the freezing of semen, but the claims are not limited to the freezing of semen. Therefore, the declaration is not commensurate in scope with the claim language and cannot be persuasive of the enablement of the instant claims. The declaration does not present any objective evidence such as a published article, that even sperm/semen can be

frozen without a cryoprotectant and thawed with retention of function (*in vitro* fertilization), much less any tissue or organ (heart, brain, lung, liver etc.), all of which fall under the scope of “biological matter”. The examples of the instant specification show only the freezing and thawing of semen/sperm with a cryoprotectant. Thus, neither the declaration nor the specification objectively demonstrate the scope of the claimed method, and there does not appear to exist a body of knowledge in the field of medical technology which would support the scope of the instant claims.

The examiner has indicated that the specification is considered to be enabling for the freezing of semen/sperm with the inclusion of a cryoprotectant; however, the claims are not so limited.

Claim Rejections – 35 USC § 103

Claims 78, 98–115, 119–123 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,873,254 [IDS].

The claims are directed to a method for changing the temperature of a sample comprising:

- (i) changing the temperature of the sample by subjecting it to a temperature gradient from an initial to an intermediate temperature,
- (ii) subjecting the sample to the intermediate temperature until the sample uniformly reaches the intermediate temperature,
- (iii) changing the temperature of the sample until it reaches a final temperature, wherein the sample exceeds 0.5 cm in at least two mutually perpendicular cross sections and wherein the initial, intermediate and final temperatures are different and all progress in either a higher or lower sequence from one another.

US 5,873,254 teaches a method of changing the temperature of a sample comprising: subjecting the sample to a temperature gradient to change the temperature of the sample from an initial temperature to an intermediate temperature, held at the constant intermediate temperature, then changing to a

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final temperature (col. 5, ls. 40–60, col. 6). The temperature is a constant -7C as the sample moves through block 14. This corresponds to maintaining the temperature by pausing the sample. Whether the temperature is maintained at an intermediate level by pausing the sled or having the block uniformly the same intermediate temperature as the sled moves through appears to be an element of experimental design because the result is the same, i.e. maintenance of the same temperature in the sample for a period of time. This reference teaches a freezing method based on directional freezing as the material is moved through a temperature gradient so that the cooling rate and ice propagation front are precisely controlled, instead of the more familiar and common multi-directional heat transfer methods.

The reference lacks the explicit stipulation of the size of the sample as exceeding 0.5cm in each of two mutually perpendicular cross-sections.

In the generic description of the invention (Summary of Invention), no limitation as to the size of the sample is described. Thus, the generic description is non-limiting with regard to size of sample.

While the size of the sample in the exemplification is ABOUT 1cm X 1cm x 0.5mm (col. 6, l. 15), use of the term “about” permits a variation of undefined range around this measurement. Please see MPEP 2144 IV A where it is stated that changes in size, shape or sequence of adding ingredients is *prima facie* obvious. Mere scaling up of a prior art process is not sufficient to patentably distinguish over the art in the absence of other evidence.

Claims 78, 98–115, 119–123 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,873,254 [IDS] in combination with US 4,131,200 [A] in light of Dayian *et al.* [V2].

The claims and US 5,873,254 have been discussed above. Also, please note that no dimensions have been stipulated which might limit the size of the

apparatus and no negative limitations have been used to limit the size of the samples used in the controlled freezing method of US '254.

US 4,131,200 discloses a bag designed for freezing biological materials such as platelets. The dimensions of the bag are 9.3 cm by 10.2 cm. The method of Dayian *et al.* was used to test the bags. Dayian *et al.* teach a PC concentration of about 57 mls, see footnote on Table 1A. A calculation of the thickness of the bag when containing a volume of 57 mls is $57 \text{ cc} = 9.3\text{cm} \times 10.2 \text{ cm} \times \text{Thickness}$. Solving for T = about 0.6 cm.

Therefore, the substitution of the controlled freezing method of laterally varying thermal gradients for the uncontrolled platelet freezing method described in US 4,131,200 would have been obvious for the advantages taught in US 5,873,254, such as improved viability of cells.

One of ordinary skill in the art would have been motivated at the time of invention to make these substitutions/variations in order to obtain the results as suggested by the references with a reasonable expectation of success. The claimed subject matter fails to patentably distinguish over the state of the art as represented by the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

DECLARATION OF A. AMIR

The declaration of A. Amir under 37 CFR 1.132 filed 11/6/08 is insufficient to overcome the rejection of claims 78, 98-115, 119-123 based upon 35 USC § 103 over US '254 as set forth in the last Office action.

A. Amir states that US '254 describes a device which is capable of producing a uniform cooling rate of $-0.1^{\circ}\text{C}/\text{min}$ through a biological sample and also describes method for the freezing of semen involving cooling the semen sample from 30°C to an "intermediate temperature" which is slightly below the lipid phase transition temperature at a rate slow enough to prevent chilling injury, preferably about $1^{\circ}\text{C}/\text{min}$. A. Amir states that the sample size

described in US '254 refers to a smaller sample size than the present sample in the instant claims. The sample size described in the exemplification of US '254 is "about 1 cm X 1 cm X 0.5mm"; however, the generic description of the method and the device used in the method are without size or dimension limitations, nor are they any teachings in the reference with regard to size limitations. Thus, while the exemplified sample size may be less than the instantly claimed sample size, this is not significantly persuasive to overcome an obviousness rejection, particularly since scaling up is *prima facie* obvious.

A. Amir states that it is his belief and understanding that the bulk of the sample being frozen is crucial and has a great effect on post thaw viability. The larger the sample the more damage it suffers. This is a function of the heat transfer properties. While this may be true, the method of the prior art reference US '254 discloses a zone of constant temperature -7°C in which the sample remains for about 10 minutes (col. 6, l. 64). The instant exemplification has a zone of constant temperature (a pause) in example 3 which is for 20 seconds and example 4, for 60 seconds. Clearly a pause of 10 minutes, which is the time period of constant intermediate temperature taught in the prior art reference would permit equilibration of the temperature in the sample as in the instant method because the time of the pause at a constant intermediate temperature is greater than the pauses (constant temperature periods) demonstrated in the instant exemplifications. Mere rephrasing or realization of concepts already taught by specific examples in the prior art is not sufficient to overcome a prior art rejection.

Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. See Titanium Metals, 778 F.2d at 780. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. See id. at 782. However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.

"The public remains free to make, use, or sell prior art... processes, regardless of whether or not they understand their complete makeup or the underlying scientific principles which allow them to operate. The doctrine of anticipation by inherency, among other doctrines, enforces that basic principle." See *Atlas Powder Co. v. IRECO Inc.* 51 USPQ2d 1943 (Fed. Cir. 1999).

While applicant has demonstrated a method for freezing larger volume semen/sperm samples with a cryoprotectant and may have presented some unexpected results, the claims are not directed to such a method and the arguments are not directed to the results presented.

Response to Arguments

Applicant's arguments filed 2/26/08 have been fully considered but they are not persuasive. Previous rebuttals may be found in the previous office actions and are not repeated.

Applicant argues that in small samples, the outer and inner zones change their temperatures essentially at the same rate and that the cited prior art does not teach subjecting the sample to an intermediate temperature until the temperature of the sample in the cross-section is uniform and equals the intermediate temperature, and thus, the presently claimed method is not a mere scaling up of the prior art method.

Please note that "essentially the same rate" is not the same rate. Essentially the same is a relative term, which only means that the rate is not the same. If a temperature change is applied from the outside of a sample, the inner temperature will equilibrate with the outer temperature at a rate which is limited by the heat transfer rate of the sample. This is true no matter what the size of the sample. This is due the thermodynamics of heat transfer during conduction and is dependent on the thermal conductivity of the sample, $k=Q/t$ times $L/A \times \Delta T$, where k is the thermal conductivity constant, Q is the quantity of heat, t is the time, L is the thickness, A is the surface area and ΔT is the change in temperature. Please notice that all samples have thickness, therefore

have positive rates of heat transfer. Only if the sample has no dimensions is heat transfer infinitely large and therefore, truly instantaneous or “the same”.

With regard to the “pausing” of the sample at one temperature or uniformity of temperature in the sample, please see col. 6, l. 64 of the prior art reference where the sample spends about 10 minutes inside block 14 at constant temperature of -7°C, then decreases the temperature again to -35°C at a rate of 0.3°C/min. This appears to be a pausing at an intermediate temperature which according to applicant’s arguments concerning heat transfer rates, would reasonably be enough time to equilibrate the sample in any cross-section. Also, in applicants arguments on page 15, applicant states that uniformity may be achieved by methods (a), (b) or (c). It appears that method (c) was exemplified in col. 6, l. 64 of the prior art reference.

RESPONSE TO ARGUMENTS filed 11/6/08

Applicant's arguments filed 11/6/08 have been fully considered but they are not persuasive.

Applicant argues that they have met the written description requirement. However, the rejection is a scope of enablement rejection not a written description rejection. Written description is separate and distinct from the enablement requirement, see MPEP 2164 and in particular 2164.03. Thus, the arguments are not persuasive of error in the rejection since the examiner has provided a quantity of objective evidence of unpredictability in the art of freezing biological material for the disclosed purpose in the specification, which objective evidence has not been persuasively rebutted by applicant.

Applicant argues that the instant claims are not merely scaling up the prior art method and that unexpectedly superior results are achieved with the presently claim subject matter. Applicants then further state the presently claimed subject matter is directed to a method for the cryopreservation of relatively large **semen** samples. Please note that applicant's arguments are not

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commensurate in scope with their arguments or the alleged superior results which are purported to have been demonstrated in the specification.

Arguments concerning the teachings of US '254 with regard to "intermediate temperature" equilibration vs. the CLAIMED method have been answered above in the response to A. Avav's declaration and in the response to arguments mailed 5/6/08. It is the examiner's carefully considered opinion that the instant claims have not overcome the cited prior art reference of US '254 which teaches the general method of decreasing the temperature of a sample using a temperature gradient, holding the sample at one temperature for the exemplified 10 minutes (col. 6, l. 64) and continuing to lower the temperature of the sample to a final temperature.

The examiner believes that there is patentable material in the instant specification, but the scope and breadth of the instant claims is not allowable for the reasons of record.

Applicant is urged to look carefully at the exemplifications in the present specification in an effort to uncover and specifically point out the unexpected results and present claims commensurate in scope with these results. Also, a decrease in the number of independent claims would simplify prosecution.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In

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no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). It is applicants' burden to indicate how amendments are supported by the ORIGINAL disclosure. Due to the procedure outlined in MPEP 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 USC 102 or 35 USC 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone number is (571) 272-0922. The examiner can normally be reached on Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, M. Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sandra Saucier/
Primary Examiner
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